REMARKS

By this Amendment, Applicant herein provides a new set of claims which more clearly define the invention and which overcome all prior rejections. The new claims are merely rewritten version of claims from the original application, and thus no new matter has been added. For reasons as stated below, Applicant submits that the present claims now overcome all previous objections and have been placed in condition for immediate allowance.

In the Official Action, the Examiner objected to the specification with regard to the lack of a Sequence Listing and references to said Sequence ID numbers. Applicant now overcomes this objection in that a sequence listing and diskette are herein provided along with amendments making proper reference to the Sequence ID numbers where appropriate.

In the Official Action, the Examiner rejected Claims 1-15 and 21 under 35 U.S.C. § 112, first paragraph, on the grounds that subject matter of the claims was not enabled by the specification so that one skilled in the art could make and/or use the present invention. In addition, the Examiner rejected the claims on the basis that the subject matter of the claims was not described in a manner that would convey that the Applicant was in possession of the claimed invention at the time the application was filed. Without addressing the merits of the Examiner's rejections as applied to the prior claims, these rejections are respectfully traversed in the present claims wherein Applicant has set forth specific information regarding the sequence and location of amino acids to be utilized at the N-terminal region, or binding region VI, in order to

achieve the benefits of the invention, namely the reduction or elimination of albumin's affinity for trace metals such as nickel or copper. As such, the skilled artisan would readily be able to practice the present invention, and it is clear that Applicant was in possession of the invention as of the time of the original filing since such claims were described in this form in the original specification.

Accordingly, the present claims are entirely proper under 35 U.S.C. §112, first paragraph, and the Examiner's rejection on the basis of this provision is traversed and should be withdrawn.

In the Official Action, the Examiner rejected Claims 1-15 and 21 under 35 U.S.C. § 103(a) on the basis of Carter US Patent 5,780,594 in light of Carter et al., "Structure of Serum Albumin", page 189. The Examiner argued that the Carter US '594 patent disclosed "changing one or more amino acids so to arrive at a serum albumin with the requisite binding properties" (Official Action, page 7), and that the Carter Serum Albumin article disclosed that "removal of the His residue in site VI . . . will greatly reduce the capacity of human serum albumin to bind trace metals. . ." However, neither of these arguments are correct, and indeed neither of the Carter prior art references, either singly or in combination, disclose or suggest the particular invention as embodied in the present claims.

With regard to Carter US Patent 5,780,594, the simple fact is that this reference does not disclose or remotely suggest the present invention, namely the specific truncations and mutations at the N-terminal region as set forth in the claims which lead to the reduction or elimination of albumin binding to trace metals such as nickel and

copper. Moreover, while the Examiner goes to great lengths in the § 112 rejection to state how one skilled in the art would not be enabled to make the specific amino acid truncations necessary for the invention ("the quantity of experimentation need is great, on the order of several man-years and then with little, if any, reasonable expectation of success", see page 3), the Examiner contrarily states that based on the simple fact that the Carter '594 patent describes that amino acids may be modified in general, "it would have been obvious to one of ordinary skill in the art . . . to have made the modifications to the amino acids sequence of human serum albumin, be it the addition of one or more amino acids or the deletion of same . . .to produce a serum albumin that has the requisite binding properties" See pages 7-8.

Regardless of these contradictory points of view, the simple fact is that the Carter '594 patent is totally silent with regard to the truncation or deletion of an amino acids, much less the specific ones called for by the claims of the present application, which would be useful in reducing or eliminating binding of albumin, in this case to trace metals such as copper of nickel. Instead, the teaching of the Carter '594 patent is that slight modifications may be made to the amino acid sequence in the relevant binding regions without reducing the binding ability of those regions, a teaching that is directly opposite to that of the present claimed invention wherein the idea is to reduce or eliminate binding to trace metals on the basis of the specific truncations as set forth in the claims.

Accordingly, the Carter '594 patent does not disclose or anywhere suggest the present invention, and actually teaches away from the present invention because it reflects that changes can be made in the binding region which will not affect the binding ability of the region in contrast to the present claims.

Moreover, the Carter "Serum Albumin" article does not disclose or suggest the present invention and thus cannot be added to the Carter '594 patent to anticipate or make obvious the present invention. In the first place, the disclosure at page 189 of the Carter article is simply an observation that canine albumin lacks histidine at position 3 and had lower affinity for nickel and copper, yet at the same time, as shown in the Bar-Or January 2001 article (*Eur. J. Biochem.* 268:42-47), there were other variations in the N-terminus which could have been responsible for the difference in binding. Accordingly, the Carter article itself does not disclose that histidine was primarily or entirely responsible for trace metal binding in human serum albumin, and clearly does not disclose or suggest preparing a human serum albumin with the specific truncations and mutations of the present claims.

Even further, as shown in the present claims, it is in fact the case that several of the truncates in accordance with the invention actually maintain the histidine, and thus, if anything, the Carter article would teach away from the present invention if interpreted to conclude that it was solely histidine that was responsible for copper binding and needed to be eliminated in all cases. Clearly, the Carter article does not disclose or suggest the invention as embodied in the present claims, but in fact teaches away from

the present claims and thus cannot be combined with the Carter '594 patent to anticipate or make obvious the present invention.

Accordingly, the Examiner's rejection on the basis of the Carter '594 patent and Carter article, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

Finally, although not a part of the present Official Action, the Applicant submitted an IDS which included references cited in the equivalent PCT prosecution of the present application. However, none of these references disclose or suggest the invention as presently claimed. For example, the cited Bar-Or reference has a publication date of January, 2001 and thus is not prior art to the present claims. The Takahashi article does not disclose or suggest the present truncations to human serum albumin, but instead relates to proalbumin which is different from human serum albumin and has different sequences, including extra residues at the N-terminal region which differentiate that reference from the present claims even further. The Ohda patent US 5,612,197 relates to the production of human serum albumin in cultures that contain at least one amino acid such as histidine, wherein the amino acid improves productivity of human serum albumin. Nowhere in the Ohda patent is there any disclosure or suggestion of the particular sequences of the present claims. Finally, the Noda patent US 5,962,649, which was cited as merely defining the general state of the art by the Examiner, relates to a specific method of purifying recombinant human serum albumin via specific heating and treating steps and thus has no bearing on the patentability of the claimed invention.

In short, Applicant submits that none of the references cited during the US prosecution or the PCT prosecution, either singly or in combination, disclose or suggest the invention as presently claimed, and that the rejection on the basis of any prior art references is respectfully traversed and should be withdrawn.

Accordingly, Applicant submits that in light of the foregoing amendments and arguments, the present application overcomes all prior objections, and is now in condition for immediate allowance. Such action is earnestly solicited.

Respectfully submitted,

April 2, 2002

B. Aaron Schulman
Registration No. 31,877

LARSON & TAYLOR, PLC
1199 North Fairfax Street, Suite 900
Alexandria, Virginia 22314
(703) 739-4900

ATTACHMENT B

Marked Up Replacement Paragraphs

At the following locations, a marked up copy of the replaced paragraph is provided.

Page 10, lines 1-17.

In accordance with the present invention, it is preferred to obtain a serum albumin having a truncation or deletion especially at the three flexible residues on the n-terminus, namely the **Asp-Ala-His** residues which are connected to the sequence Lys-Ser-Glu at the n-terminal region. In a particularly preferred embodiment of the invention, the desired albumin sequence will have a single amino acid truncation which removes the **Asp** residue at the n-terminal end and which will thus have the sequence **Ala-His**-Lys-Ser-Glu (SEQ ID NO: 1). . . This embodiment is particularly preferred because it is least likely to produce an antigenic response yet should significantly reduce trace metal binding at the n-terminal end. Similarly, deletions or truncations of a size greater than a single amino acid are also contemplated by the invention, and will also result in an improved albumin which is less likely to bind to metals such as copper and nickel. Accordingly, other n-terminal deletions in the region of the three flexible residues at the n-terminal end are also suitable in the invention, and thus n-terminal sequences such as His-Lys-Ser-Glu (SEQ ID NO: 2). . . and Lys-Ser-Glu. . . will also be useful in the modified albumin of the invention. Additionally, any other further truncation of the n-terminal end that is sufficient so as to either sterically hinder the binding site VI or eliminate vital binding interactions at that region will be suitable as a modified albumin in accordance with the invention.

Page 10, line 18 to Page 11, line 2.

In addition, other suitable forms of the present invention will include those additions or substitutions of the amino acid sequence at the n-terminal region or the binding site VI which are sufficient to disrupt the binding of trace metals such as copper and nickel to the albumin, either by providing sufficient steric hindrance to inhibit metal binding or by disrupting or eliminating vital binding interactions. For example, any suitable leader sequence or other elongation at the n-terminal sequence **Asp-Ala-His**-Lys-Ser-Glu (SEQ ID NO: 3). . . will be useful to provide a modified albumin in accordance with the invention.

Page 11, lines 3-12.

Furthermore, in another preferred embodiment in accordance with the invention, any substitutions at the histidine residue at position 3 will also produce an improved non-metal binding modified albumin because the histidine is a critical aspect of the copper and nickel binding. The preferred substituted modified albumin sequence in accordance with the invention thus has the sequence **Asp-Ala-X**-Lys-Ser-Glu (SEQ ID NO: 4). . ., wherein X represents any amino acid substitution (or insertion or deletion) which will provide steric hindrance or disrupt vital binding interactions sufficient to reduce or eliminate the binding of metals such as copper and nickel to the serum albumin. Because of the critical nature of the histidine at position 3, any amino acid insertions in the leader sequence before this histidine will generally be sufficient to disrupt the metal binding.

Page 15, lines 3-11:

Addition of the following amino acids to the n-terminus, Glu-Ala-Glu-Phe-**Asp-Ala-His** **(SEQ ID NO: 5)**, in the recombinant albumin identified as NCP control number A99-13,2393) resulted in greatly reduced coloration of the purified recombinant albumin. This albumin was prepared by conventional recombinant means normally used to obtain albumin from nucleic acids with the nucleic acids being recombined so as to have a sequence coding for the mutated albumin (either directly or through degenerate sequences). The reduction in coloration reflects the reduction in the bound trace metals and was quantitatively demonstrated by the reduction in A_{400} for the albumin of the invention versus normal rHSA when produced and purified under otherwise identical conditions.